AMENDMENTS TO THE CLAIMS

This claim listing will replace all prior versions, and listings, of the claims in the application.

Listing of the Claims:

1. (currently amended) An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence comprising the sequence set forth in SEQ ID NO: 3;

(b) a nucleotide sequence encoding the polypeptide set forth in SEQ ID NO: 4;

(c) a nucleotide sequence which hybridizes under highly stringent conditions to the complement of the coding sequence of (a) or (b), wherein said stringent conditions comprise a final wash with 0.015 M sodium chloride and 0.0015 M sodium citrate at 65-68°C in 0.1x SSC and 0.1% SDS or 0.015 M sodium chloride, 0.0015M sodium citrate, and 50% formamide at 42°C, which encodes a polypeptide having E3α ligase activity of the polypeptide set forth in SEQ ID NO: 4; and

(d) a nucleotide sequence fully complementary to any of (a)-(c).

2. (currently amended) An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence encoding a polypeptide that is at least ~~about 70, 75, 80, 85,~~ 90~~, 95, 96, 97, 98, or 99~~ percent identical to a polypeptide comprising the sequence set forth in SEQ ID NO: 4, wherein the encoded polypeptide has ~~an~~ E3α ligase activity of the polypeptide set forth in SEQ ID NO: 4;

(b) ~~a nucleotide sequence encoding an allelic variant or splice variant of the nucleotide sequence as set forth in SEQ ID NO: 3;~~

~~(c)~~ a nucleotide sequence comprising a fragment of the nucleotide sequence of SEQ ID NO: 3; (a); or (b) encoding a polypeptide fragment of at least about 25

amino acid residues, wherein the encoded polypeptide fragment has ~~an~~ E3α ligase activity of the polypeptide set forth in SEQ ID NO: 4;

[[(d)]] (c) a nucleotide sequence comprising a fragment of at least about 25 nucleotides of the nucleotide sequence of SEQ ID NO: 3, or any of (a)-[[(c)]] (b) ~~comprising a fragment of at least about 16 nucleotides~~;

[[(e)]] (d) a nucleotide sequence which hybridizes under highly stringent conditions to the complement of the coding sequence of any of (a)- [[(d)]] (c), wherein said stringent conditions comprise a final wash with 0.015 M sodium chloride and 0.0015 M sodium citrate at 65-68°C in 0.1x SSC and 0.1% SDS or 0.015 M sodium chloride, 0.0015M sodium citrate, and 50% formamide at 42°C; and

[[(f)]] (e) a nucleotide sequence fully complementary to any of (a)- [[(e)]] (d).

3. (currently amended) An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence encoding a polypeptide set forth in SEQ ID NO: 4 with ~~at least one~~ 1 to 100 conservative amino acid ~~substitution~~ substitution(s), wherein the polypeptide has ~~an~~ E3α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 4;

(b) a nucleotide sequence encoding a polypeptide set forth in SEQ ID NO: 4 with ~~at least one~~ 1 to 100 ~~conservative~~ amino acid ~~insertion~~ insertion(s), wherein the polypeptide has ~~an~~ E3α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 4;

(c) a nucleotide sequence encoding a polypeptide set forth in SEQ ID NO: 4 with ~~at least one~~ 1 to 100 ~~conservative~~ amino acid ~~deletion~~ deletion(s), wherein the polypeptide has ~~an~~ E3α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 4;

(d) a nucleotide sequence encoding a polypeptide set forth in SEQ ID NO: 4 which has a C- and/or N-terminal truncation up to about 100 amino acids, wherein the

polypeptide has ~~an~~ E3α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 4;

(e) a nucleotide sequence encoding a polypeptide set forth in SEQ ID NO: 4 with ~~at least one~~ a modification of 1 to 100 amino acids ~~selected from the group~~ consisting of amino acid substitutions, amino acid insertions, amino acid deletions, C-terminal truncation, and N-terminal truncation, wherein the polypeptide has ~~an~~ E3α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 4;

(f) ~~a nucleotide sequence of (a)-(e) comprising a fragment of at least about 16 nucleotides;~~

~~(g)~~ a nucleotide sequence which hybridizes under highly stringent conditions to the complement of the coding sequence of any of (a)- [[(f)]] (e), wherein said stringent conditions comprise a final wash with 0.015 M sodium chloride and 0.0015 M sodium citrate at 65-68°C in 0.1x SSC and 0.1% SDS or 0.015 M sodium chloride, 0.0015M sodium citrate, and 50% formamide at 42°C, wherein the nucleotide sequence encodes a polypeptide which has E3α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 4; and

[[(h)]] (g) a nucleotide sequence fully complementary to any of (a)-(e).

4. (original) A vector comprising the nucleic acid molecule of claims 1, 2, or 3.

5. (original) A host cell comprising the vector of claim 4.

6. (original) The host cell of claim 5 that is a eukaryotic cell.

7. (original) The host cell of claim 5 that is a prokaryotic cell.

8. (currently amended) A process of producing a ~~huE3α~~ human E3α ubiquitin ligase polypeptide comprising culturing the host cell of claim 5 under suitable conditions to express the polypeptide, and optionally isolating the polypeptide from the culture.

9. (canceled)

10. (currently amended) The process of claim 8, wherein the nucleic acid molecule comprises promoter DNA other than the promoter DNA for the native ~~huE3α~~ human E3α ubiquitin ligase polypeptide operatively linked to the DNA encoding the ~~huE3α~~ human E3α ubiquitin ligase polypeptide.

11. (original) The isolated nucleic acid molecule according to claim 2 wherein the percent identity is determined using a computer program selected from the group consisting of GAP, BLASTP, BLASTN, FASTA, BLASTA, BLASTX, BestFit, and the Smith-Waterman algorithm.

12-45. (canceled)

46. (original) A composition comprising a nucleic acid molecule of claims 1, 2, or 3 and a pharmaceutically acceptable formulation agent.

47. (original) A composition of claim 46 wherein said nucleic acid molecule is contained in a viral vector.

48. (original) A viral vector comprising a nucleic acid molecule of claims 1, 2, or 3.

49-58. (canceled)

59. (currently amended) A diagnostic reagent comprising a detectably labeled polynucleotide encoding the amino acid sequence set out in SEQ ID NO: 4; or a fragment of at least about 25 amino acid residues of the amino acid sequence set out in SEQ ID NO: 4, variant or homolog thereof ~~including allelic variants and spliced variants thereof~~.

60. (previously presented) The diagnostic reagent of claim 59, wherein said labeled polynucleotide is a first-strand cDNA.

61. (withdrawn - currently amended) A method for ~~determine~~ determining the presence of ~~huE3α~~ human E3α ubiquitin ligase nucleic acids in a biological sample comprising the steps of:

(a) providing a biological sample suspected of containing ~~huE3α~~ human E3α ubiquitin ligase nucleic acids;

(b) contacting the biological sample with a diagnostic reagent according to claim 59 under conditions wherein the diagnostic reagent will hybridize with ~~huE3α~~ human E3α ubiquitin ligase nucleic acids contained in said biological sample;

(c) detecting hybridization between ~~huE3α~~ human E3α ubiquitin ligase nucleic acid in the biological sample and the diagnostic reagent; and

(d) comparing the level of hybridization between the biological sample and diagnostic reagent with the level of hybridization between a known concentration of ~~huE3α~~ human E3α ubiquitin ligase nucleic acid and the diagnostic reagent.

62. (withdrawn - currently amended) A method for detecting the presence of ~~huE3α~~ human E3α ubiquitin ligase nucleic acids in a tissue or cellular sample comprising the steps of:

(a) providing a tissue or cellular sample suspected of containing ~~huE3α~~ human E3α ubiquitin ligase nucleic acids;

(b) contacting the tissue or cellular sample with a diagnostic reagent according to claim 59 under conditions wherein the diagnostic reagent will hybridize with ~~huE3α~~ human E3α ubiquitin ligase nucleic acids;

(c) detecting hybridization between ~~huE3α~~ human E3α ubiquitin ligase nucleic acid in the tissue or cellular sample and the diagnostic reagent; and

(d) comparing the level of hybridization between the tissue or cellular sample and diagnostic reagent with the level of hybridization between a known concentration of ~~huE3α~~ human E3α ubiquitin ligase nucleic acid and the diagnostic reagent.

63. (withdrawn) The method of claim 59 wherein said polynucleotide molecule is DNA.

64. (withdrawn) The method of claim 59 wherein said polynucleotide molecule is RNA.

65-66. (canceled)

I. Preliminary Remarks and Explanation of Amendments

By the foregoing, the Applicants have amended the specification at page 8, line 31, to correspond to Figures 1A-1L, which have replaced original Figure 1 to satisfy drawing requirements.

Claims 1-8, 10, 11, 46-48, and 59-64 are pending and were variously rejected under 35 U.S.C. §102 and §112, first paragraph (enablement and written description) and second paragraph. Claims 61-64 were withdrawn from consideration.

Claim 1 has been amended to recite the stringent conditions necessary for hybridization, along with E3α ubiquitin ligase activity, thus providing structural and functional characteristics sufficient to identify members of the claimed genus. Support in the specification for the recited hybridization conditions is found at page 14, line 27, through page 16, line 20. Support in the specification for E3α ubiquitin ligase activity is found throughout the specification, including at page 2, line 8 through page 4, line 14. Claim 1 has also been amended to recite that the nucleotide sequence of subpart (c) hybridizes under expressly recited highly stringent conditions to the complement of the coding sequence of (a) or (b). The specification teaches stringent hybridization conditions and cites references for describing well-known techniques implementing those conditions (*see* page 14, line 27, through page 16, line 20). Claim 1 has been further amended to recite that the nucleotide sequence of subpart (d) is fully complementary any of (a)-(c). Support in the specification for "fully complementary" sequences is found throughout the specification, including at page 11, lines 27-31.

Claim 2 has been amended to recite a nucleotide sequence encoding a polypeptide comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 4, wherein the encoded polypeptide has E3α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 4, thus providing structural and functional characteristics sufficient to identify members of the claimed genus. Support in the specification for a human E3α ubiquitin ligase polypeptide that is at least 90% identical to the amino acid sequence of SEQ ID NO: 4 is found throughout the specification, including at page 11, lines 9-15. Support in the specification for E3α ubiquitin ligase activity is found

throughout the specification, including at page 2, line 8 through page 4, line 14. Claim 2 has also been amended to recite that the nucleotide sequence of subpart (e) hybridizes under expressly recited highly stringent conditions to the complement of the coding sequence of any polynucleotide of (a)-(d). Claim 2 has been further amended to recite that the nucleotide sequence of subpart (f) is fully complementary to any polynucleotide of (a)-(d). Support in the specification for "fully complementary" sequences is found throughout the specification, including at page 11, lines 27-31. In addition, claim 2 has been amended to include fragments of the nucleotide sequence of SEQ ID NO: 3 of at least about 25 nucleotides. Support in the specification for fragments of about 25 nucleotides is found throughout the specification, including at page 11, lines 16-31.

Claims 2 and 59 have been amended to remove reference to allelic and splice variants in order to expedite prosecution.

Claim 3 has been amended to recite a nucleotide sequence encoding a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 4 with modifications of one to 100 amino acids consisting of amino acid substitutions, amino acid insertions, amino acid deletions, and C- and/or N- terminal truncations up to about 100 amino acids, wherein the polypeptide has E3α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 4, thus providing structural and functional characteristics sufficient to identify members of the claimed genus. Support in the specification for variants of human E3α ubiquitin ligase polypeptide with modifications of from 1 to 100 amino acids is found throughout the specification, including at page 17, lines 14-32. Support in the specification for E3α ubiquitin ligase activity is found throughout the specification, including at page 2, line 8 through page 4, line 14. In addition, claim 3 has been amended to remove subpart (f), which claims fragments of the nucleotide sequences of (a)-(e) of at least about 16 nucleotides. Claim 3 has also been amended to recite that the nucleotide sequence of subpart (f) hybridizes under expressly recited highly stringent conditions to the complement of the coding sequence of any polynucleotide of (a)-(e). Claim 3 has been further amended to recite that the nucleotide sequence of subpart (f) is fully complementary to any polynucleotide of (a)-(e). Support in the specification for "fully complementary" sequences is found throughout the specification, including at page 11, lines 27-31.

Claims 8, 10, 61, and 62 have been amended to replace the abbreviated term "huE3α" with the unabbreviated term "human E3α ubiquitin ligase." Support for this amendment is found throughout the specification, including at page 1, lines 9-10. Claim 61 has also been amended to correct a typographical error.

Claim 59 also has been amended to recite that the diagnostic reagent may comprise polypeptide fragments of the amino acid sequence set out in SEQ ID NO: 4 that are at least about 25 amino acid residues in length. Support for this amendment is found throughout the specification, including at page 16, line 30, through page 17, line 13.

No new matter is introduced by the amendments herein. Support for the amendments is found throughout the specification and the original claims as filed.

The Applicants do not intend, with these or any other amendments, to abandon the subject matter of claims previously presented, and reserve the right to pursue such subject matter in duly filed continuing patent applications.

II. The Rejection Under 35 U.S.C. §102 Should Be Withdrawn.

The Examiner rejected claims 3-8, 10, 11, 46-48, 59, and 60 under 35 U.S.C. §102(b) as assertedly being anticipated by Kwon et al., *Proc. Natl. Acad. Sci. (U.S.A.)* 95:7898-7903, 1998 (reference C5 of record; hereinafter "Kwon"). Office Action at page 10. Kwon was characterized as teaching the mouse ortholog of human ubiquitin ligase E3α polypeptide, which assertedly consists of 1757 amino acids and is 45.8% identical to SEQ ID NO: 4. Based on that characterization, the Examiner asserted that the DNA which encodes the protein thereof will encode "polypeptides having the amino acid sequence as set forth in SEQ ID NO: 4 with at least one conservative or any substitution, insertion, deletion, truncation, or the combination of the above or as variant or homolog thereof." *Id.* In response, the Applicants traverse.

To invalidate a claim as anticipated under 35 U.S.C. §102, a single reference must disclose each and every feature recited in the claim sought to be invalidated. *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991).

The Applicants have amended the claims to exclude the subject matter described by Kwon. For example, the nucleotide sequence of Kwon does not disclose, expressly or inherently, each and every feature recited in the amended claims. Kwon's mouse E3α ubiquitin ligase polynucleotide sequence fails to anticipate a nucleotide sequence encoding a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 4 with modifications of one to 100 amino acids consisting of amino acid substitutions, amino acid insertions, amino acid deletions, and C- and/or N- terminal truncations up to about 100 amino acids, and will not hybridize to SEQ ID NO: 4 under the highly stringent conditions recited in claim 3. Therefore, Kwon does not disclose each element of claim 3 and cannot anticipate the subject matter of that claim. In addition, Kwon's polynucleotide sequence fails to anticipate a polynucleotide encoding the amino acid sequence set out in SEQ ID NO: 4; or a fragment of at least about 25 amino acid residues of the amino acid sequence set out in SEQ ID NO: 4, variant or homolog thereof recited in claim 59. Because Kwon's mouse E3α ubiquitin ligase polynucleotide sequence does not disclose each element of claim 59, it cannot anticipate the diagnostic reagent of claim 59. Thus, Kwon does not disclose each element of either of independent claims 3 or 59.

As a matter of law, a dependent claim incorporates each limitation of a claim from which it depends. 35 U.S.C. §112, fourth paragraph. Claims 4-8, 10, and 46-48 depend from claim 3. Claim 60 depends directly from claim 59. Each of these rejected dependent claims thus ultimately depends from one of independent claims 3 and 59 and, as established above, Kwon does not disclose each element of either of those independent claims. Accordingly, Kwon cannot disclose, expressly or inherently, each element of any of dependent claims 4-8, 10, 46-48, and 60 and, for that reason, Kwon does not anticipate the subject matter of any of those dependent claims.

Claim 11, however, depends from claim 2, which was not rejected under Kwon in the Office Action. Moreover, the Applicants submit that the Examiner has not provided a reason for rejecting claim 11 under 35 U.S.C. §102(b) over Kwon, and Kwon's mouse E3α ubiquitin ligase polynucleotide sequence fails to satisfy: 1) the 90% identity limitation of claim 2 (a); 2) the fragment limitations of claim 2(b) or (c); and 3) the hybridization limitations recited in claim 2(d). Therefore, Kwon does not disclose each

element of claim 2. For that reason, the Applicants request that the rejection of claim 11 under Kwon be withdrawn.

Thus, Kwon fails to disclose, expressly or inherently, each limitation of any one of the rejected claims, as amended. Accordingly, Kwon fails to anticipate the subject matter of any of the rejected claims. For these reasons, the rejection of claims 3-8, 10, 11, 46-48, 59, and 60 under 35 U.S.C. §102(b) over Kwon has been overcome and should be withdrawn.

III. The Rejection Under 35 U.S.C. §112, First Paragraph, Should Be Withdrawn.

Enablement

The Examiner rejected claims 1-8, 10-11, 46-48, and 59-60 under 35 U.S.C. §112, first paragraph, for asserted lack of enablement. The claims were rejected for assertedly not providing enablement for the broad scope of the claims, which encompass a nucleotide sequence encoding a polypeptide having an amino acid sequence at least 70, 80, 85, 90, or 95% identical to the amino acid sequence of SEQ ID NO: 4, and which retain E3α ubiquitin ligase activity, a nucleotide sequence encoding a polypeptide having an amino acid sequence at least 70, 80, 85, 90, 95, 96, 97, 98, or 99% identical to the amino acid sequence of SEQ ID NO: 4 and having no known activity, as well as a nucleotide sequence that hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 3 that has no known activity or has E3α ubiquitin ligase activity. The Examiner also rejected the claims for encompassing polypeptides having no defined activity or having E3α ubiquitin ligase activity that is encoded by a nucleotide sequence that hybridizes under highly stringent conditions to SEQ ID NO: 1. The Examiner then addressed Wands factors (*see In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)) as factors to be considered in determining whether undue experimentation is required. Office Action at pages 6-8. The Applicants respectfully traverse this rejection and submit that the claims, as originally filed, are fully enabled by the specification.

The enablement requirement of 35 U.S.C. §112, first paragraph, ensures that an application teaches how to make and use the invention as claimed without requiring undue

experimentation. The inquiry may be guided by consideration of several factors enumerated in a biotechnology context in *In re Wands*.

Claims 1-3 have been amended by defining the claimed sequences with a combination of structural and/or functional characteristics taught in the specification. For example, claim 1(c) has been amended to recite the stringent conditions necessary for hybridization, along with E3α ubiquitin ligase activity, thus providing structural and functional characteristics of the claimed polynucleotides. Claim 2 has been amended so that the variants all possess a recited sequence relationship to SEQ ID NO: 4, namely "at least 90 percent identical to the amino acid sequence of SEQ ID NO: 4, wherein the polypeptide has E3α ligase activity of the polypeptide set forth in SEQ ID NO: 4." The application teaches one how to make and use such variants without undue experimentation (*see* the specification at page 27, line 29, through page 33). The application describes methods of determining identity and similarity, and teaches methods of making conservative and non-conservative amino acid modifications. For example, the application explains how conservative modifications to the amino acid sequence (and the corresponding modifications to the encoding nucleotides) will produce human E3α ubiquitin ligase polypeptides having functional characteristics similar to those of naturally occurring human E3α ubiquitin ligase polypeptides. Claim 3 has been amended to recite an isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 4 with modifications of one to 100 amino acids consisting of amino acid substitutions, amino acid insertions, amino acid deletions, C-terminal truncations, and/or N-terminal truncations up to about 100 amino acids, wherein the polypeptide has E3α ubiquitin ligase activity of the polypeptide having the sequence set forth in SEQ ID NO: 4, thus providing structural and functional characteristics of the claimed molecules.

Given the base sequence information (e.g., SEQ ID NOS: 3 and 4), the specifically identified activity of the molecules (*i.e.*, E3α ubiquitin ligase activity), and the well-known techniques for detecting such activity, the Applicants submit that one skilled in the art would be able to identify and make the claimed variants of the native human E3α ubiquitin ligase using no more than routine experimentation. The application also describes variants and methods of identifying variants (*see* the specification including at least at page

17, line 14, through page 21, line 18; and at page 27, line 29, through page 33). The application includes methods of determining identity and similarity, and teaches methods of making conservative and non-conservative amino acid modification. For example, the application explains how conservative modifications to the amino acid sequence (and the corresponding modifications to the encoding nucleotides) will produce human E3α ubiquitin ligase polypeptides having functional characteristics similar to those of naturally occurring human E3α ubiquitin ligase polypeptides. Figure 1 also provides an alignment of the amino acid sequences for human and murine E3α ubiquitin ligases I and II and, thus, identifies regions of the polypeptides that are highly conserved. Moreover, assays to detect or measure human E3α ubiquitin ligase activity are disclosed in the specification, especially in Example 7.

In view of the foregoing comments and the amendments to the claims, the Applicants submit that claims 1-8, 10-11, 46-48, and 59-60 are fully enabled by the present specification and the rejection of the claims under 35 U.S.C. §112, first paragraph, for lack of enablement should be withdrawn.

Written Description

The Examiner rejected claims 1-8, 10-11, 46-48, and 59-60 under U.S.C. §112, first paragraph, for an asserted lack of written description. Office Action at pages 3-6. The Examiner has asserted the following reasons for rejection: 1) claim 1(c) is drawn to a nucleotide sequence which hybridizes under highly stringent conditions to the complement of (a) or (b) and, therefore, is drawn to a highly variable genus of nucleotide sequences encompassing those encoding polypeptides having E3α ubiquitin ligase activity and polypeptides with an unknown activity; 2) claim 2(b) recites "an allelic or splice variant" of SEQ ID NO: 3 and claim 59 recites a "polynucleotide encoding the amino acid sequence set forth in SEQ ID NO: 4 or a fragment, variant or homolog thereof including allelic variants and splice variants thereof" while the specification teaches only one allele within the scope of the genus; 3) claim 3 recites polypeptides having the amino acid sequence set forth in SEQ ID NO: 4 "with at least one conservative or any substitution, insertion, deletion, truncation, or the combination of the above without limiting the number of modifications" and, thus, fails to provide a sufficient description of the claimed genus in structure and function to identify

members of the genus; and 4) the specification fails to provide any structure:function correlation present in all members of the claimed genus.

The Examiner relied on *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) whereby a claimed genus must (1) fully describe at least one species whereby one of skill, in view of the prior art, could predict the structure of other species encompassed by the claimed genus, and (2) identify the common characteristics of the claimed molecules. The Applicants respectfully traverse this rejection and submit that the claimed subject matter, as originally filed, is adequately described in the specification.

To satisfy the written description requirement under 35 U.S.C. §112, first paragraph, the application as filed must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ.2d 1111 (Fed. Cir. 1991); *see also* M.P.E.P. §2163 (I). Moreover, the initial burden of establishing a *prima facie* case of lack of written descriptive support is on the Office. M.P.E.P. §2163 (II). The Applicants submit that the Patent Office has not met this burden. Moreover, the rejection is now moot in consideration of the amendments to the claims.

To expedite prosecution, the Applicants have 1) amended claims 2 and 59 to remove reference to allelic or splice variants; 2) amended claims 2 and 3 to recite the specific polypeptide activity as being "E3α ligase activity"; 3) amended claim 2 to specify nucleotide sequences encoding a polypeptide that shares at least 90% identity with the amino acid sequence of SEQ ID NO: 4 **and** has E3α ligase activity; 4) amended claim 3 to include a limitation on the number of modifications that can be made to the polypeptide having the amino acid sequence of SEQ ID NO: 4 in combination with E3α ligase activity; and 5) amended claims 1 and 3 to include the specific hybridization conditions necessary for defining members of the claimed genus and to recite the specific polypeptide activity as having "E3α ligase activity." These amendments provide structural and functional attributions to define members of the claimed genus and to distinguish molecules that are not species of that genus, thereby rendering moot the rejection.

Further, Figure 1 provides an alignment of the amino acid sequences for human and murine E3α ubiquitin ligases I and II and, thus, identifies regions of the polypeptides that are highly conserved. Further, conservative amino acid substitutions in polypeptides and the redundancy of the genetic code are well-known facts in the art that are effectively described by reciting "variants." Taken together, one of skill in the art would recognize that the Applicants were in possession of the claimed genus.

In summary, the Applicants submit that amended claims 1, 2, 3, and 59 are described sufficiently for one of skill to reasonably conclude that the inventors were in possession of the claimed subject matter as of the relevant filing date. As set out in Section I above, there is support in the specification for all of the amendments herein. Consequently, the rejections under 35 U.S.C. §112, first paragraph, of claims 1, 2, 3, and 59 for lack of written description have been overcome-in-part and are rendered moot-in-part by the amendments to the claims, and the rejections should be withdrawn for these claims and all claims which depend from them.

In view of the foregoing comments and the amendments herein, the rejection of claims 1-8, 10, 11, 46-48, 59, and 60 under 35 U.S.C. §112, first paragraph, for lack of written description should be withdrawn.

IV. The Rejection Under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn.

Claims 1-8, 10, 11, 46-48, 59, and 60 were rejected under 35 U.S.C. §112, second paragraph, as assertedly being indefinite. Specifically, the claims were rejected for assertedly: 1) reciting "highly stringent conditions" in claims 1 and 3 and defining these conditions by non-limiting examples, rendering the metes and bounds of the claims unascertainable (pages 14-16 of the specification); 2) not defining the degree of complementarity in claims 1 and 3; 3) reciting "the complement thereof" when "hybridizes to SEQ ID NO: 3" is sufficient because SEQ ID NO: 3 comprises coding sequence and its complement; 4) not defining the activity in claims 2 and 3; 5) confusing language in claim 2 because SEQ ID NO: 3 is an entire sequence and it cannot comprise only a fragment thereof; 6) reciting "variant or homolog" in claim 59 when neither term is assertedly defined in the specification and each has multiple different definitions in the art; and 7) depending on

rejected base claims. In response, the Applicants respectfully traverse this rejection. Moreover, this rejection is moot in consideration of the amendments to the claims.

Claims 1 and 3 have been amended to provide specific conditions required for stringent hybridization. Claims 1-3 also have been amended to recite that the degree of complementarity covered in these claims is "full" complementarity. Claims 1 and 3 have been further amended to encompass sequences which hybridize under the recited stringent conditions to the complement of the coding sequences of (a) or (b) in claim 1 or (a)-(e) in claim 3. Claims 2 and 3 have been amended to recite that the polypeptide of SEQ ID NO: 4 has E3α ubiquitin ligase activity. Claim 2 has been amended to recite "a fragment of the nucleotide sequence of SEQ ID NO: 3." Claim 59 has been amended to remove reference to allelic or splice variant to expedite prosecution. However, the Applicants submit that the terms "variant" and "homolog" are not indefinite and are described throughout the specification, including at least at page 17, line 14, through page 21, line 18, and at page 34, lines 5-8. Moreover, the application also describes variants and methods of identifying variants (*see* the specification at page 27, line 29, through page 33). The application also describes methods of determining identity and similarity, and teaches methods of making conservative and non-conservative amino acid modifications. For example, the application describes how conservative modifications to the amino acid sequence (and the corresponding modifications to the encoding nucleotides) will produce human E3α ubiquitin ligase polypeptides having functional characteristics similar to those of naturally occurring human E3α ubiquitin ligase polypeptides.

Therefore, the amendments to claims 1, 2, 3, and 59, as set out above, have rendered moot the rejections under 35 U.S.C. §112, second paragraph, as applied to these claims. In incorporating the limitations of the base claims from which they depend, the dependent claims rejected on this ground are also definite for the reasons provided above. Accordingly dependent claims 4-8, 10, 11, 46-48, and 60 have been clarified by the amendments to claims 1, 2, 3, and 59.

In view of the foregoing comments and the amendments herein, the rejection of claims 1-8, 10, 11, 46-48, 59, and 60 under 35 U.S.C. §112, second paragraph, should be withdrawn.